



# A cognitive behavioral perspective about attitude, perception and acceptability of vaccination against human papilloma virus

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## ABSTRACT

**Background:** Cervical cancer is one of the most common malignancies among young sexually active females worldwide. The most common cause of cervical cancer is human papillomavirus infection which is sexually transmitted. It can be prevented by human papillomavirus vaccines. The uptake of the vaccine is still low despite the promising results of the vaccine. **Aim:** The aim of our study is to assess the level of awareness regarding Human papillomavirus vaccination and to determine the barriers that limit the vaccination among females in Saudi Arabia. **Methods:** A descriptive cross-sectional study conducted on 18 September 2018 until 7 May 2019, at King Khalid University Hospital, Riyadh, Saudi Arabia. A sample size of 382 adult Saudi females collected from three clinics which are gynaecology, family medicine and paediatrics clinic by electronic questionnaire through an email invitation, which was validated by a pilot study. Descriptive statistic was performed using SPSS version 22. Ethical approval number KSUMC/IRB-02/875123. **Results:** Among 382 respondents, 319 (83.5%) are aware of cervical cancer, however, a low percentage of them knew the cause. The rate of HPV awareness is (18.6%). More than half of the respondents are not sure whether the HPV vaccine can prevent cervical cancer or not. The main barriers for no vaccination were lack of awareness (73%) and concerns about the side effects (56%). **Conclusion:** Most of the respondents lack knowledge about HPV and its vaccination. It's recommended to increase awareness by conducting public awareness programs and applying policies regarding the vaccine.

**Keywords:** Awareness; Barriers; Human Papilloma Virus; Vaccination; Saudi Women

## 1. INTRODUCTION

Cervical cancer is one of the most common malignancies among young sexually active females worldwide, about half a million women are diagnosed each year and over 250,000 of them die (Darwish et al., 2014). The prevalence of cervical cancer in Saudi Arabia is increasing; it is ranked as the 8th most common cancer (Hoque et al., 2013). The most common cause of cervical cancer is the human papillomavirus. This virus is also known for causing genital warts, this variation in disease depends on the type of the virus. High risk HPV types (16, 18) and low risk HPV types (6, 11). This virus can be transmitted sexually and non-sexually such as a transmission from women to newborn infants during childbirth (Doshi et al., 2015). HPV types 16 and 18 are responsible for 70% of cervical cancer (Almazrou et al., 2020). HPV infection can be prevented by HPV vaccines (Ghamri et al., 2020). There are three types of HPV vaccines bivalent, quadrivalent, and non-valent, the quadrivalent vaccine is also efficacious in preventing genital warts, which is caused by HPV types 6 and 11 (Yaghoobi et al. 2019; Al-Ghamdi et al., 2020). HPV vaccines are administered intramuscularly in a three-dose series. High-quality studies done by Global Advisory Committee on Vaccine Safety (GAVCS), showed that this vaccine is well tolerated and there is no major adverse event reported, most of them were mild like injection site-related pain, swelling, and erythema (Alsbeih et al., 2014; Petrosky et al., 2015). The incidence of cervical cancer among young women decreased by 50% in countries that have been implemented HPV vaccination to their immunization program effectively. Despite the effectuality and the promising results of the vaccine, its uptake remains low. In 2010 Saudi Arabia approved the vaccine for females better between the ages of 11-26 years (Hussain et al., 2016).

In 2006, many countries have implemented HPV vaccination programs as a preventable intervention against cervical cancer and other HPV related diseases (Bruni et al., 2016). Since that, there are studies have been done to assess the level of awareness and to identify the barriers affect HPV vaccines uptake worldwide. HPV vaccine uptake worldwide is (1.4%), which is relatively low and there are a number of studies suggest some barriers that may play a role. Taking into consideration socioeconomic status as a barrier, a study was conducted in United States on 23,564 adolescent's shows HPV series completion was low among those living below the poverty level in comparison with those who live at or above the poverty level (Simms et al., 2020). Health care provider plays an important role in the vaccine uptake, in a cross-sectional study that conducted in the US found that Pediatricians are more likely to recommend the vaccine, whilst family physicians were the least likely to recommend it (Vadaparampil et al., 2011; Alreshidi et al., 2020). Parents have an influence on their children vaccination, parental refusal due to safety concerns is found to be a significant barrier in a cross-sectional study conducted in China, Hong Kong over 720 surveys (Wong et al., 2013). Study was conducted in 2015 on female university students found that maternal education affects the likelihood of vaccination (Lefkowitz et al., 2014). Regarding the level of awareness, a study was conducted in Bangladesh through a self-administered questionnaire among 160 females professionals employed, found that 98% of them heard about cervical cancer, however only half of them knew that HPV infection as a cause of cervical cancer, and about 2% of them were vaccinated against HPV vaccines (Bhuiyan et al., 2018). In Saudi Arabia there is a recent study discussed the attitudes and perceptions toward HPV vaccination through a questionnaire which was administered using an interview-based model, the result shows (31.7%) Saudi women were aware of human papillomavirus, and only (24.6%) were aware of HPV as an etiology for most cases of cervical cancer. In the same study (29.9%) of them knew that cervical cancer and other HPV-related morbidities can be prevented by HPV vaccines (Hussain et al., 2016; Mahomed et al., 2020).

There are many studies addressing cervical cancer and HPV vaccination, however the uptake of HPV vaccines still considered low in Saudi Arabia. The aim of our study is to assess the level of awareness regarding HPV vaccination and to determine the barriers that limit taking the vaccines among females in Saudi Arabia.

## 2. METHODS

### Study design

We conducted a descriptive cross-sectional, questionnaire-based study at ambulatory care clinics of Obstetrics and Gynecology, Family Medicine, and Pediatrics at King Khalid University Hospital, Riyadh, Saudi Arabia. The study period was from 18 September 2018 until 7 May 2019. Ethical approval number is KSUMC/IRB-02/875123.

### Sample selection (description of population and sample frame)

A sample size of 382 respondents was calculated based on published studies to detect awareness and barriers of HPV vaccine among Saudi females. The inclusion criteria were Saudi female patients aged between 18 and 60 years. We excluded males and children. Ethical approval had been obtained from Institution of Review Board, College of Medicine, King Saud University.



### Method of questionnaire administration

Questionnaire was distributed electronically through email invitation by the research chairs of the university hospitals. The sample was almost equally collected from the three clinics. The data was collected through an electronic questionnaire in the period between 13 January and 7 February 2019. All respondents received an electronic attached consent form (Arabic and English) sent through email with the questionnaire to be filled and signed simultaneously before filling the questionnaire and they were informed about the purpose and the details of the study.

Moreover, they were informed about their right to withdraw at any time without obligation towards the study team. The questionnaire contained three sections. The first section is a socio-demographic data such as (age, socioeconomic status, residency, level of education, and income). The second section included questions that assess the awareness of HPV infection in relation to cervical cancer and knowledge about the HPV vaccine. The third section contained questions regarding the barriers that prevent them from taking the HPV vaccine.

### Evidence of reliability and validity

We set up the construct validity for the questionnaire. Validity is the degree to which the questionnaire tests what it wants to test. One of the simplest ways to evaluate construct validity is to offer the metric to two parties, one of which is reported to have better knowledge than that of the other category. Also we measure the internal consistency reliability which is the propensity of accuracy observed in repetitive observations of the same phenomena is referred to as precision. Internal consistency relates to the degree to which all objects on a scale evaluate the various facets of the same element. Cronbach's alpha is often used to determine the efficacy of dietary awareness assessments with questions which have more than two correct answers. Cronbach's alpha varies from  $r=0$  to 1, with  $r=0.7$  or more assumed to be fairly accurate. We also measured test-retest reliability which involved Administration of the same calculation to the same category of questionnaire-takers under the same circumstances on two separate occasions and similarity of scores. The reliability coefficient is essentially the association (commonly the Pearson correlation) here between results of the first and subsequent measures. The Pearson coefficient estimate may be between zero (no correlation) and one (ideal correlation).

### Statistical analysis and verifying data entry

Continuous variables were expressed as mean  $\pm$  standard deviation and categorical variables were expressed as percentages. The t-test was used for continuous variables. The Cronbach's alpha was used to assess the reliability and internal consistency of the items in the questionnaire. We performed a validation study on 21 respondents, to assess the validity and reliability of the questionnaire. Descriptive statistic performed to assess the level of awareness and to determine the major barrier for low vaccine uptake this had been applied in each section. P value of  $<0.05$  was considered statistically significant and 95% confidence interval was used to report the statistical significance and precision of results. The data collected from each respondent's answers is coded numerically. Responses have been transformed to 1 and 0 for true and false replies, accordingly ('not applicable or I don't know' responses have also been coded). A variety of statistical tests have been carried out to determine the feasibility and efficiency of the survey. The student t-test was used to assess significant differences between the mean category ( $p<0.001$ ). The Chi-square method was used to assess whether the age and gender proportions differed significantly between the two classes ( $p<0.05$ ).

### Measures to reduce response bias

To avoid non-response bias we sent a pre-notification email with information about the survey to come. We sent a personalized invite and a reminder to avoid response bias. We asked neutrally worded questions and our answer options were not leading. Survey was anonymous. We reduced our order bias. We reduce the number of scale questions to the bare minimum and grouped our survey by topic and leaved demographic questions until later in the survey. We asked question that engage respondents. We randomized our question and answer options.

## 3. RESULTS

The number of study respondents was 382 women. The Questionnaire filled by the respondents from the three clinics, (OBGYN 131, Pediatric 126, Family medicine 125). The majority of the age groups 26 – 45 years (70.6%). Overall, 97.1% of the respondents are Saudi and 2.9% are non-Saudi. Regarding the educational level, most of the respondents 254(66.5%) were university educated, the rest were undergraduate and below (25.9% secondary, 3.7% intermediate, 2.1% primary, 1.8% illiterate).



### Construct validity

Females who were Saudis scored consistently higher than the non-Saudis in the other group on both sections of the questionnaire ( $p < 0.001$ ). The females who have children had an average score (mean $\pm$ SD) of (12.7 $\pm$ 7.4). The scores ranged from 2 to 18 in the group of females who have children and 0 to 16 in the other group. The students who were Saudis answered more questions correctly (6.5 $\pm$ 1.8) compared to the other group (3.5 $\pm$ 2.4). When the same research was conducted out for era, level of education, monthly income, it was noticed that the difference in age didn't significantly affect the results. Accordingly, the questionnaire fulfilled the requirement for construct validity.

### Internal consistency

The Cronbach alpha values in both classes were distinct. Values (individual and cumulative) for females who did not know about the vaccine were higher than for the other category. When all females were weighed, the alpha values were 0.83. The alpha value of the final test was 0.90.

### Test-retest reliability

Reliability test Pearson's correlation coefficient was based on the ratings of respondents (88 females who knows about the vaccine and 114 females who did not know) who answered the questionnaire twice. The correlation coefficients ranged across the parts and the two female groups (from 0.69 to 0.87). Total reliability was high ( $r = 0.90$ ,  $p < 0.001$ )

Out of the total respondents, 89% were either employee or household. According to monthly income, most of the respondents are relatively from low socioeconomic status (79.6 %). In regard to the marital status, majority of the respondents were married 317(83%), 41(10.7%) were single, 14(3.7%) were divorced, and 10(2.6%) are widowed. Out of these 301(78.8%) respondents had children (Table 1).

**Table 1** The Socio demographic characteristics of the participants (n=382).

characteristics	No. (%)
Age	
18-25y	71 (18.6)
26-36y	177 (46.3)
36-45y	93 (24.3)
46-55y	34 (8.9)
56-65y	7 (1.8)
Nationality	
Saudi	371 (97.1)
Non-Saudi	11 (2.9)
Living in Riyadh	
Yes	348 (91.1)
No	34 (8.9)
Educational level	
Illiterate	7 (1.8)
Primary	8 (2.1)
Intermediate	14 (3.7)
Secondary	99 (25.9)
University and above	254 (66.5)
Occupation	
Student	42 (11.0)
Employee	140 (36.6)
Household	200 (52.4)
Monthly income	
<5000 SR	149 (39.0)
5000-10000 SR	155 (40.6)
10000-20000 SR	68 (17.8)
>20000 SR	10 (2.6)



Marital status	
Married	317 (83.0)
Single	41 (10.7)
Widow	10 (2.6)
Divorced	14 (3.7)
You have children	
Yes	301 (78.8)
No	81 (21.1)
Smoking	
Yes	8 (2.1)
No	374 (97.9)

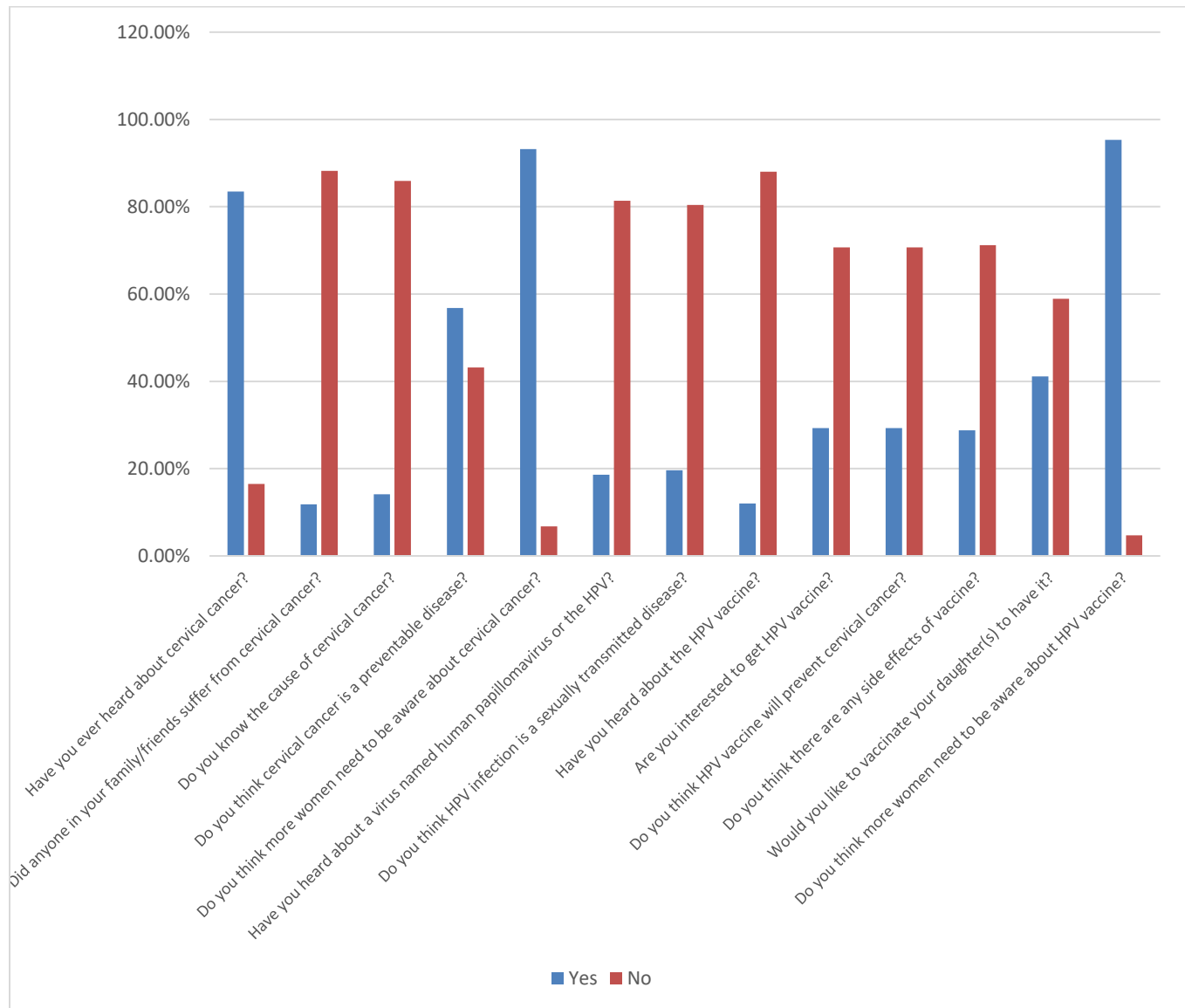
A total of 83.5% were aware about cervical cancer and only 16.5% were unaware. However, only 14.1% of the respondents know the cause of cervical cancer. Around, half of the participants answered that cervical cancer is a preventable disease. Only 11.8% have a family member or a friend diagnosed with cervical cancer. Most of the respondents 356(93.2%) thought that women need to be more aware of cervical cancer (Table 2 & figure 1).

**Table 2** Cervical cancer Knowledge and vaccine of HPV.

Knowledge	Yes N (%)	No N (%)	I don't know N (%)
1- Have you ever heard about cervical cancer?	319(83.5)	63(16.5)	
2- Did anyone in your family/friends suffer from cervical cancer?	45(11.8)	337(88.2)	
3- Do you know the cause of cervical cancer?	54(14.1)	328(85.9)	
4- Do you think cervical cancer is a preventable disease?	217(56.8)	24(6.3)	141(36.9)
5- Do you think more women need to be aware about cervical cancer?	356(93.2)	26(6.8)	
6- Have you heard about a virus named human papillomavirus or the HPV?	71(18.6)	311(81.4)	
7- Do you think HPV infection is a sexually transmitted disease?	75(19.6)	46(12.0)	261(68.3)
8- Have you heard about the HPV vaccine?	46(12.0)	336(88.0)	
9- Are you interested to get HPV vaccine?	112(29.3)	89(23.3)	181(47.4)
10- Do you think HPV vaccine will prevent cervical cancer?	112(29.3)	19(5.0)	251(65.7)
11- Do you think there are any side effects of vaccine?	110(28.8)	19(5.0)	253(66.2)
12- Would you like to vaccinate your daughter(s) to have it?	157(41.1)	36(9.4)	189(49.5)
13- Do you think more women need to be aware about HPV vaccine?	364(95.3)	18(4.7)	

As for human papillomavirus (HPV), 18.6% were aware about it. Among the respondents, 68.3% don't know that HPV infection is a sexually transmitted disease. The majority of the respondents had low knowledge about HPV vaccine. More than half of the respondents 65.7% were not sure whether HPV vaccine can prevent cervical cancer or not. However, 29.3% believed that cervical cancer could be prevented by the HPV vaccine. The present findings showed that 66.2% don't know if there are any side effects of the vaccine. The willingness to get the vaccine was reported by 29.3% of them, while 47.4% were not sure if they will get the vaccine or not. 49.5% of the respondents didn't know whether to vaccinate their daughters or not. Most of the respondent 364(95.3%) agreed that they need more awareness about the HPV vaccine (Table 2).

In regards to the barriers, the main barrier was lack of awareness as 279(73%) of the respondents didn't know about the vaccine and 103(27%) knew about the vaccine. The concern about the side effect was identified as a barrier among 56%. The effectiveness of the vaccine was a potential barrier in 44.5%. Women who never had sex (13.1%) thought that they don't need to take the vaccine. Overall, 94.5% of the respondents agreed that they didn't get a doctor's recommendation about the vaccine. Accessibility to get the vaccine was a barrier among 20.4% of the respondents. A small percentage (10.5%) thought that they aren't within the recommended age to get the vaccine. Believe and trust on vaccination was a barrier among 35.3%. About 10.5% answered that they don't need to get the vaccine because they were already diagnosed with HPV infection. Fear of needles was rarely identified as a barrier (Table 3).



**Figure 1** Cervical cancer Knowledge and vaccine of HPV.

**Table 3** Barriers of not taking HPV vaccine.

Barriers of not taking HPV vaccine	Yes	No	I don't know
	N (%)	N (%)	N (%)
1- Don't know about the vaccine	279(73.0)	103(27.0)	
2- Concern about side effects	214(56.0)	168(44.0)	
3- Worried about effectiveness	170(44.5)	84(22.0)	128(33.5)
4- Don't have sex, don't need vaccine	50(13.1)	48(12.6)	284(74.3)
5- Parents wouldn't let me get vaccine	23(6.0)	144(37.7)	215(56.3)
6- Doctor didn't recommend I get the vaccine	361(94.5)	21(5.5)	
7- Too expensive	42(11.0)	5(1.3)	335(87.7)
8- Don't like shots/needles	70(18.3)	312(81.7)	

9- Don't have access to doctor that offers vaccine	78(20.4)	11(2.9)	293(76.7)
10- Outside recommended age range	40(10.5)	77(20.2)	265(69.4)
11- Too inconvenient to get vaccine series	50(13.1)	91(23.8)	241(63.1)
12- Don't trust vaccines	135(35.3)	247(64.7)	
13- Already diagnosed with HPV	40(10.5)	342(89.5)	

The association between the demographic characteristics of the participants with the knowledge and barriers of HPV vaccination represents that there was no statistical significance between the mean knowledge and the different age groups, educational level, monthly income, and marital status. A significant association was only found between the mean knowledge score and the nationality, Saudi participants has a higher knowledge score. No statistical significance was observed between the mean score of the barriers and the demographic characteristics except for having children, as higher score was among those women who have children (Table 4).

**Table 4** Mean of total score for Knowledge and Barriers of HPV among Saudi Women.

Variables	Knowledge <sup>¶</sup> Mean ±SD	P-value	Barriers <sup>  </sup> Mean± SD	P-value
Age				
18-25y	5.34±2.74	0.581	3.99±2.36	0.910
26-35y	5.17±2.21		4.00±1.73	
36-45y	5.47±2.65		4.19±2.01	
46-55y	5.59±2.54		4.12±1.74	
56-65y	6.43±1.27		4.43±2.15	
Nationality				
Saudi	5.38±2.45	0.049*	4.09±1.94	0.105
Non Saudi	3.91±1.58		3.27±1.49	
Educational level				
Illiterate	5.43±2.30	0.900	3.43±1.90	0.309
Primary	5.50±1.93		5.13±1.55	
Intermediate	5.29±2.61		4.29±2.05	
Secondary	5.12±2.27		3.85±1.85	
University and above	5.41±2.53		4.12±1.96	
Monthly income				
<5000 SR	5.01±2.30	0.158	3.99±1.95	0.511
5000-10000 SR	5.54±2.52		4.22±1.89	
10000-20000 SR	5.47±2.46		3.96±2.03	
>20000SR	6.20±2.94		3.50±1.58	
Marital status				
Married	5.39±2.48	0.678	4.14±1.95	0.120
Single	5.21±2.32		3.55±1.87	
Widow	4.60±1.78		4.30±1.06	
Divorced	4.93±2.40		3.21±1.63	
You have children				
Yes	5.46±2.53	0.064	4.17±1.92	0.032*
No	4.89±2.05		3.65±1.92	

\* Significant p-value<sup>¶</sup> Total score for the knowledge = 13 (yes = 1, no or I don't know = 0) high score means high knowledge <sup>||</sup> Total score for the Barriers = 13 (yes = 1, no or I don't know = 0) high score means more Barriers.



## 4. DISCUSSION

Cervical cancer is the 8th most common malignancy in Saudi Arabia (Sausa et al., 2018). Most common cause of cervical cancer is HPV. The infection can be prevented by HPV vaccination which was approved by Saudi Food and Drug Authority in 2010 (Altamimi et al., 2020). The aim of our study is to assess the awareness and the barriers of HPV vaccination to encourage health care providers to take actions. The incidence and prevalence of HPV infection in Saudi Arabia compared to other countries considered low, this could be due to cultural and religious background or it could be due to insufficient national data.

In this study, while the majority of the respondents know about cervical cancer (83%), the knowledge in the aspects of HPV infections and vaccination was very low. Only (18%) know about HPV and (85%) of the respondents didn't recognize HPV infection as one of the causes of cervical cancer. This result consistent with a study conducted in Saudi Arabia among female university students, there was a knowledge deficit in the risk factors of cervical cancer with (26.9%) of theme considered HPV infection as a risk factor for cervical cancer (Bednarczyk et al., 2010). Another study conducted among women in Saudi Arabia, also found that there was a lack of knowledge regarding HPV (16.4%) (Holman et al., 2014).

Most of the respondents in this study didn't know that HPV infection is sexually transmitted (80%). On the other hand, a study conducted among females in United Arab Emirates, (63%) of the respondents recognized that HPV infection is a sexually transmitted (Samara et al., 2015). A significant number of respondents in this study (88%) have never heard about the HPV vaccine. Moreover, (56%) of the respondents in this study agreed that cervical cancer is preventable, at the same time (65%) of them were not sure if HPV vaccine will prevent cervical cancer or not. Similarly, knowledge of the HPV vaccine as the primary prevention of cervical cancer is very poor in a study conducted among Saudi female university students (Altamimi et al., 2020). High population in this study were married (83%), (78.8%) have children, and nearly half of them (49.5%) were not sure if they will vaccinate their daughter/s. A study included 301 parents in Thailand, indicates that the respondents had a high acceptance and willingness to vaccinate their children and parents with greater knowledge had higher acceptance of the vaccine (Al-Shaikh et al., 2014).

The major and the most significant barrier in this study was the lack of awareness of HPV vaccine (73%). According to a previous study in Saudi Arabia, the most common determinants affecting HPV vaccination are knowledge and physician's recommendation (Riza et al., 2020). Concern about the side effects was also identified as an important barrier in this study (56%). More than half of the respondents (64%) from health Sciences University in Malaysia were also concerned about the side effects of HPV vaccine, which could be one of the major barriers worldwide (Ortashi et al., 2013).

Doctor's recommendation was a barrier in (95%) of the respondents in this study. A study conducted in the Kingdom of Saudi Arabia stated that women are more likely to get the vaccine if their health care providers recommend it to them (Grandahl et al., 2018). Vaccine cost appears to be an important barrier for its acceptance which was found in one of the studies conducted among Saudi female students. In contrast, (87%) of the respondents in this study were not sure about the cost of the vaccine. Furthermore, other barriers in this study were difficult to be clearly assessed, which is possibly due to low knowledge in many aspects of the HPV vaccine. In the present study, (10%) of the women were already diagnosed with HPV infection. In our point of view, this is considered a high percentage and it may be because of misconception between HPV infection and other cervical or vaginal infection (Rajiah et al., 2015).

Although the majority of the respondents (66.5%) were well-educated in this study, there was no statistical significant between knowledge score and educational level and this reflects the lack of general reproductive health education. The opposite was in another study in KSA, the Knowledge about HPV was significantly higher among university and higher education level. In this study, a high percentage of the participants (70.6%) were between 24-45 ages. However, no significant association was found between the age groups and the knowledge score (Grandahl et al., 2018). In contrast to study conducted in UAE, where the knowledge score was significantly associated with age (Grandahl et al., 2018). In the same study, no significant association was noticed between marital status and knowledge scores which are compatible with the results in this study. The statistical significant that observed between the knowledge score and Nationality in this study, is most likely due to small percentage of non-Saudis.

One of the study limitations, the sample subjects were exclusively from one hospital (KKUH) which may not present the whole population very well, so further studies needed in the future to be conducted in multiple hospitals to present the general population adequately. Also there was difficulty in finding statistical estimation in the aspects of HPV infection and vaccination in Saudi Arabia.

## 5. CONCLUSION

Our study assessed barriers in addition to awareness of HPV vaccination in the general population. It shows a very low level of knowledge and awareness about HPV and its association to cervical cancer, also it was noticed in the knowledge about HPV vaccination and its effectiveness in protection against HPV infection. The main barrier among women in this study was lack of awareness. Based on the results, we recommend conducting public awareness programs by establishing educational campaigns



across the country and awareness programs for girls in schools and colleges, mass media could help by presenting information about HPV and the vaccine in a wide range. Ministry of health could help by making vaccine more accessible and available in hospitals. New and culturally acceptable policies need to be developed to encourage physicians for more recommendation of HPV vaccination.

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### Author Contributions

Yasser Sabr, Doaa W. Abdulfattah, conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript. Ohoud A. Alboqami, Nouf S. Alogaily, designed the data collection instruments, collected data, carried out the initial analyses, reviewed and revised the manuscript. Nouf S. Alogaily, Thikrayat A. Omar, conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. Nehal B. Beyari and Razan S. Alotaibi approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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This study has not received any external funding.

### Conflict of Interest

The authors declare that there are no conflicts of interests.

### Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

### Ethical approval

The study was approved by the Medical Ethics Committee of King Saud University (ethical approval code: IRB/KSU897643).

### Data and materials availability

All data associated with this study are present in the paper.

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